Journal of Medical Hypotheses and Ideas (2012) 6, 75–79

Available online at www.sciencedirect.com

Journal of Medical Hypotheses and Ideas

journal homepage: www.elsevier.com/locate/jmhi

REGULAR ARTICLES

Interleukin-25 as a candidate gene in immunogene therapy of pancreatic cancer

Zahra Piri [a], Abdolreza Esmaeilzadeh [b,*], Mehri Hajikhanmirzaei [c]

[a] Students Research Committee, Faculty of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran
[b] Department of Immunology, Faculty of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran
[c] Noor Molecular Diagnosis Laboratory, Zanjan, Iran

Received 18 April 2012; revised 24 August 2012; accepted 24 August 2012

KEYWORDS

Pancreatic cancer;
IL-25;
Mesenchymal stem cells;
Apoptosis;
Syngeneic mice model;
Immunotherapy

Abstract Pancreatic cancer is an aggressive type of malignancy. Generally, its promotion and progression are due to the disturbance in some cellular and molecular mechanisms, particularly deregulation of programmed cell death or apoptosis. Certainly, loss of counterbalance between generation and cell death will lead to the tumoural mass development in various tissues, such as pancreas.

From earlier decades, a variety of treatments as chemotherapy, radiation and surgery have been employed in order to pancreatic cancer remedial purposes, which are associated with infirm medical outcome. Therefore, with regard to the anti-cancerous and pro-apoptotic properties of the cytokine interleukin-25 (IL-25), the authors intend to anticipate a new therapeutic strategy. IL-25 – known as IL-17E – is one of the major factors responsible for death receptor-mediated pathway. Broadly, its receptor is located on multifarious cells such as pancreatic cancerous cells. We proposed to select four groups of C57BL/6 mice, for IL-25 gene inoculation, via mesenchymal stem cells as a vector, in order to increase exposure of cancerous cells to IL-25. IL-25 could activate apoptotic mediators including tumour necrosis factor receptor associated factor (TRAF6), Fas-Associated protein with Death Domain (FADD) and caspases consequently. Probably this method will be efficient in pancreatic malignancy treatment, via inducing apoptosis in pancreatic tumoural cells.

Abbreviations: IL-25, cytokine interleukin-25; PDAC, pancreatic ductal adenocarcinoma; TRAF, TNFR-associated factor; TRADD, tumour necrosis factor receptor associated death domain; TNFR, tumour necrosis factor receptor; MSC, mesenchymal stem cell; RPMI, Roswell Park Memorial Institute; PBS, phosphate buffered saline; ELISA, enzyme-linked immunosorbent assay; MHC, major histocompatibility complex; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labelling

* Corresponding author. Address: Department of Immunology, Zanjan University of Medical Sciences, Mahdavi Blv., Zanjan, Iran. Tel.: +98 9121414281.
E-mail address: a46reza@zums.ac.ir (A. Esmaeilzadeh).

2251-7294
URL: www.tums.ac.ir/english/
doi:http://dx.doi.org/10.1016/j.jmhi.2012.08.003

Introduction

Worldwide, pancreatic cancer is the eighth and ninth leading cause of death in males and females, respectively [1], and estimated incidence of pancreatic cancer is 0.39% in females and 0.56% in males in the Iranian population [2]. Approximately 95% of exocrine pancreatic cancer cases are ductal [3]. Furthermore, just 5% of patients can survive 1–5 years after treatment [4]; therefore it is noted as one of the most life-threatening cancers. Cancer of the pancreas often develops without early symptoms, although, generally, pain, anorexia, early satiety, sleep problems and weight loss are present in advanced stages of malignancy [5].

As previously mentioned, pancreatic cancer frequently initiates in the ducts that transmit digestive enzymes to the small intestine, typically recognised as ductal adenocarcinoma (DAC). Tumour development and progress of pancreatic ductal adenocarcinoma (PDAC) as well as resistance to most oncology therapies involve the absence of a reaction to apoptotic stimuli [3].

Activation of the Kirsten rat sarcoma viral oncogene homologue (KRAS) has been indicated in more than 90% of pancreatic cancers and KRAS mutation represents one of the earliest genetic alterations in pancreatic carcinogenesis [6]. In addition, mutation or deregulating of several genes such as *p53*, *p16*, *DPC4/smad4*, *SFN*, *miR-15a* and *FN1* genes in patients with pancreatic cancer have been shown [7–10], although the use of these genes as biomarkers for prognosis and therapeutic purposes is still little known and deserves more study [11]. In addition, the major role of *p53* and *p16* genes in apoptosis control is well established and dysfunction of these genes definitely will lead to a malignant lump in the pancreas [12,13]. On the other hand, it is proved that disruption of apoptosis is one of the major characteristics of pancreatic tumoural cells and other types of cancer [14,15].

Likewise, inflammatory processes, cytokines and oxidative stress play an important role in this malignancy and increase disease risk [16,17]. Research has illustrated reduction in cellular antioxidant level in chronic pancreatitis and pancreatic cancer [18].

Poor response to common treatments such as chemotherapy, radiotherapy and surgery with dismal prognosis made us to evaluate a new treatment strategy for pancreatic cancer. In fact, it is necessary to develop an impressive treatment with the minimum side effects alongside the highest efficiency [19,20]. Recently, Furuta et al. discovered that interleukin-25 (IL-25) can be used as a cytokine against breast tumoural cells, via its receptors at these cell surfaces. IL-25 is a member of the IL-17 family of pro-inflammatory cytokines and some of its biologic effects have been discovered recently [21]. The IL-25 locus is on chromosome 14, (14q11-12) [22], and has been shown to play a critical role in the initiation and propagation of the Th2 immune response [23–25], Research about IL-17E (IL-25) has demonstrated that its function is meaningfully different from the other family members and its overexpression is associated with type 2 responses by major histocompatibility complex (MHC) class II [26], alongside elevated IL-4, IL-5 and IL-13 [27,28].

The IL-25 receptor is similar to the receptors of other members of the IL-17 family [29,30], such as IL-17RA and IL-17RB [30–33], and is located on the cells of pancreas, prostate [29,30,32], kidney [32], lung [34] and liver [29]. With respect to recent investigations, IL-25 has an apoptotic effect in breast tumoural cells and could eliminate tumoural cells without any effect/impact on the intact cells. IL-25 operates very specifically and just eliminates cancerous cells with the least complications. Due to this fact that, these cells express abundant amounts of IL-25 receptors, but the blood level of IL-25 is reduced for unknown reasons [21].

IL-25 signalling pathway

It has been proved that TRAF6 family proteins play a crucial part, in various cell signalling pathways. For example, TRAF6

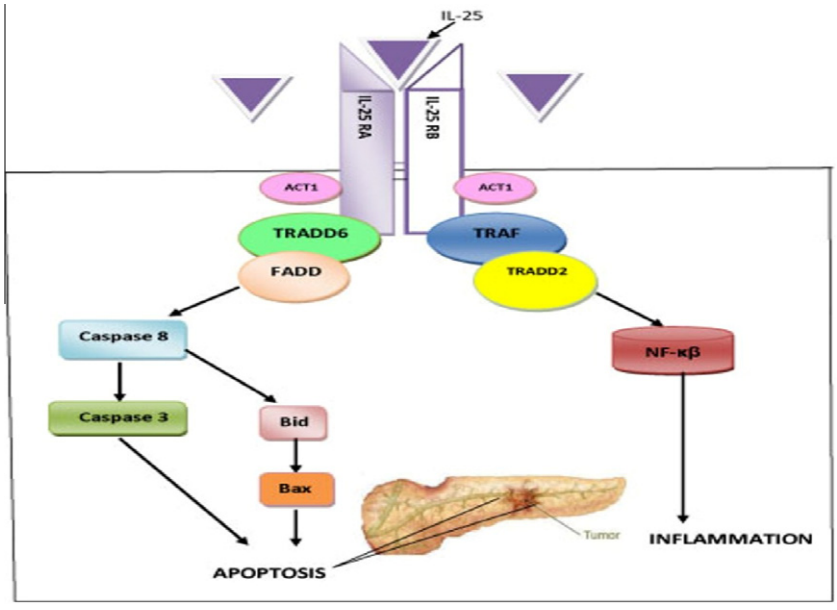

Figure 1 This schematic shows the expression of IL25R on pancreatic tumoral cells that induces apoptosis via recruiting of TRADD, TRAF6 and FADD.

exhibits important functions in regulating adaptive and innate immunity, bone metabolism and cell apoptosis [35]. Moreover, tumour necrosis factor receptor associated death domain (TRADD can activate an apoptosis pathway [36,37]. TRADD connects to the death domain of Fas-Associated protein with Death Domain (FADD), and then caspase-8 pathway will be initiated [38] (Fig. 1).

Hypothesis

Although pancreatic cancer is one of the most aggressive types of cancers, its treatment has not succeeded, due to the higher resistance to usual treatment such as surgery, radiation and chemotherapy. Therefore, the authors, taking advantage of animal modelling and immune gene therapy, suggest a novel strategy in pancreatic cancer treatment.

As IL-25 binding to its receptor leads to apoptosis of cancerous cells, it can also be used to treat pancreatic cancer [39], because one of the main causes of pancreatic cancer is resistance to apoptosis [40].

Considering the fact that, pancreatic tumoural cells produce the IL-25 receptor, but do not express IL-25 [41], the injection of IL-25 gene into the animal model as gene therapy, via mesenchymal stem cells (MSCs), can increase the malignant cells' exposure with an optimal IL-25, and lead to apoptosis of pancreatic tumoural cells.

Evaluation of hypothesis

(1) A total of 40 female C57BL/6 mice (8–10 weeks old) are prepared [42]. The first group ($n = 10$) contains control animals, which do not receive any injection. The remaining mice are divided into three categories of 10 animals per group, including the following:
   (a) Ten mice are selected for Panc02 cell line inoculation subcutaneous (s.c.) in the right hind flank [-43], in order to induce a tumour without IL-25 transfection.
   (b) The next group encompasses mice that are manipulated with IL-25 gene via bone marrow-derived cells (MSCs).
   (c) Finally, the last group contains receivers of MSCs without the IL-25 gene.

(2) The Panc02 (Panc02 is a murine ductal pancreas adenocarcinoma cell line that was established in 1984 in female C57BL/6 mice) cell line is cultured in Roswell Park Memorial Institute medium (RPMI) with 10% foetal bovine serum and 2 mM L-glutamine, 100 U ml^{-1} penicillin and 100 μg ml^{-1} streptomycin and incubated at 37 °C with 5% CO_2 in a humidified atmosphere [44].

(3) Thirty mice are anaesthetised using a mixture of ketamine/xylazine, the control mice do not receive injection. A total of 5×10^5 Panc02 cells in 50 μl phosphate buffered saline (PBS) are inoculated in the flank of mice to induce pancreatic cancer [43]. The mice are euthanised 14 days after inoculation.

(4) Comparison of tumour size and pathologic aspects of tumour cells with immunohistochemical and haematoxylin and eosin staining methods in both control and mice treated with IL-25 in terms of its impact on the growth cease of cancerous cells and reduction in tumour size [22,45].

(5) Isolation of MSCs from 6–8 week-old C57BL/6 mice. C57BL/6 mice are killed by cervical dislocation. Bone marrow is collected from the tibia and the femur of mice. A total of 70×10^6 bone marrow cells from one donor are obtained [46,47]. Then, 25×10^6 cells are prepared [47] and suspended in Dulbecco's modified Eagle's medium (DMEM) containing 15% foetal bovine serum (FBS), penicillin and streptomycin. After 24 h, cells are washed and non-adherent cells, which mostly are haematopoietic stem cells, removed. Adherent cells are cultured in complete medium for 1 week until they covered 80–90% of the bottom of the culture bottle. MSCs, from passage 4, are used in the subsequent experiments. Mature MSCs are determined by their ability to differentiate into adipocytes and osteocytes. Further properties are based on the expression of surface markers such as CD34, CD44, Stem Cell Antigen-1 (Sca-1) and Vimentin Cell Adhesion Molecule-1 (Vcam-1) [46–48].

(6) Use of MSCs of C57BL/6 mice as a vector for IL-25 gene transfection into 10 mice by the lipofection method. (This transplantation is distinguished as a syngeneic system: A transplantation in which donor and receiver are genetically identical.)

(7) To measure levels of IL-25 in blood, in the four groups via enzyme-linked immunosorbent assay (ELISA), the apoptotic tumour cells in the tumour tissues are characterised by the terminal deoxynucleotidyl transferase-mediated deoxyuridine use of tri-phosphate nick-end labelling (TUNEL) test to assay DNA fragmentation, as a marker of apoptosis [49].

Conclusion and discussion

In this hypothesis, with regard to the significance of pancreatic cancer, authors have attempted to propose an efficient, particular and affordable treatment with the least complications. The prior remedies such as antioxidant therapy could not have an effect on chronic pancreatitis which leads to pancreatic cancer [17]. As disturbance in apoptosis has a major role in pancreatic cancer promotion, treatment of this malignancy could be performed using apoptosis induction [50].

IL-25, via binding to its receptor, leads to activation of cell death pathways in tumoural cells, because IL-25R strongly interacted with FADD and TRADD (IL-25R contains a death domain (DD)-like segment).

These results indicate that IL-25 binding to its receptor increases the stability of the IL-25R-associated complex, which includes FADD and TRADD. This complex then triggers the activation of caspases 8 and 3 sequentially for apoptotic signalling [21].

As a result, we could utilise this pathway, in induction of apoptosis in cells that posses receptors of IL-25 on their surface, including pancreatic cancer cells.

In this hypothesis, we suggest pancreatic cancer treatment with use of MSCs, as a vector to transfer the IL-25 gene into mice. As indicated, MSCs possess certain features such as homing capabilities in a wide range of pathological conditions, easy expansion in culture and multi-lineage potential. They also seem

to be relatively immunoprivileged due to their expression of MHCI, but lack MHCII and the co-stimulatory molecules CD80, CD86 and CD40. These characters make MSCs suitable as a vector to transport anti-cancerous drugs [51].

As a whole, the IL-25/IL-25R signalling pathway may act as a new therapeutic object for pancreatic cancer. The cytokine IL-25 wisely attacks only the cancer cells but not the normal cells. It seems that IL-25 can operate as a stimulator cytokine, in a mouse model of pancreatic cancer cell death.

We could conclude that use of IL-25 immunogene therapy probably operates as a novel treatment in a mouse model, and in the next step could lead to design a new clinical trial about this strategy and its outcome in humans.

Overview Box

First Question: What do we already know about the subject?

From 1998, the pancreatic cancer rate has been increasing by 0.8% in men and by 1.0% in women each year. Nowadays, there is not any efficient technique for prognosis of pancreatic cancer and the common treatments are not beneficial, because pancreatic cancer is usually detected after it has spread beyond the pancreas.

Second Question: What does your proposed theory add to the current knowledge available, and what benefits does it have?

According to Furuta's discovery, which revealed that malignant mammary epithelial cells express plenty of IL-25 receptors which respond to IL-25 secreted by other non-malignant mammary epithelial cells (MECs), which induces caspase-mediated apoptosis in cultured breast cancer cells with IL-25R, but had no detrimental effect on non-malignant cells, the authors proposed that IL-25 could be effective and advantageous in apoptosis of pancreatic tumoural cells.

Third question: Among numerous available studies, what special further study is proposed for testing the idea?

To test this hypothesis, initially pancreatic tumoural cells are induced in a mouse model via MSCs. Then, investigator could assess how the cells will respond to the treatment with IL-25 by means the methods of measurement of pathologic properties and biomarkers in blood levels.

After proving the response to treatment, in a mouse model, the injection of IL-25 gene into patient could be performed.

Conflict of interest

The authors report no conflicts of interest.

References

[1] Jemal A, Bray F, Melissa M, Ferlay J, Ward E, Forman D. Global cancer statistics. Cancer J Clin 2011;61:69–90.

[2] Jamali A, Kamgar M, Massarrat S, Sotoudeh M, Larijani B, Adler G, et al.. Pancreatic cancer: state of the art and current situation in the Islamic Republic of Iran. Govaresh 2009;14:189–97.

[3] Samm N, Werner K, Ruckert F, Detlev Saeger H, Grützmann R, Pilarsky C. The role of apoptosis in the pathology of pancreatic cancer. Cancer 2011;3:1–16.

[4] Klein AP. Genetic susceptibility to pancreatic cancer. Mol Carcinog 2012;51:14–24. http://dx.doi.org/10.1002/mc.20855.

[5] DiMagno EP. Pancreatic cancer: clinical presentation, pitfalls and early clues. Ann Oncol 1999;10:140–2.

[6] Yu S, Lu Z, Liu C, Meng Y, Ma Y, Zhao W, et al.. miRNA-96 suppresses KRAS and functions as a tumor suppressor gene in pancreatic cancer. Cancer Res 2010;70:6015–25.

[7] Bulathsinghala P, Syrigos KN, Saif MW. Role of vitamin D in the prevention of pancreatic cancer. IJNAM 2010;2010:721365. http://dx.doi.org/10.1155/2010/721365.

[8] Chen R, Pan Sheng, Crispian DA, Brentall TA. Gene expression and proteomic analysis of pancreatic cancer: a recent update. Cancer Genomics & Proteomics 2006;3:1–10.

[9] Zhang XJ, Ye H, Zeng CW, He B, Zhang H, Chen YQ. Dysregulation of miR-15a and miR-214 in human pancreatic cancer. Hematol Oncol 2010;3:46.

[10] Grochola LF, Taubert H, Greither T, Bhanot U, Udelnow A, Wurl P. Elevated transcript levels from the MDM2 P1 promoter and low p53 transcript levels are associated with poor prognosis in human pancreatic ductal adenocarcinoma. Pancreas 2011;40:265–70.

[11] López-Casas PP, López-Fernández LA. Gene-expression profiling in pancreatic cancer. Expert Rev Mol Diagn 2010;10:591–601.

[12] Kim JY, Lee KS, Seol1 JE, Yu K, Chakravarti D, Seo SB. Inhibition of p53 acetylation by INHAT subunit SET/TAF-Ib represses p53 activity. Nucleic Acids Res 2012;40:175–87. http://dx.doi.org/10.1093/nar/gkr61.

[13] Amaral JD, Castro RE, Sola S, Steer CJ, Rodrigues CMP. P53 is a key molecular target of ursodeoxycholic acid in regulating apoptosis. J Biol Chem 2007;282:34250–9.

[14] Fulda S. Exploiting apoptosis pathways for the treatment of pancreatic cancer. Curr Signal Transduct T 2009;4:1–5.

[15] Jia-hua Z, Hai-yan C, Ze-qian Y, Dao-wei H, Zheng P, De-tong Y. Resveratrol induces apoptosis in pancreatic cancer cells. Chin Med J Peking 2011;124:1695–9.

[16] Farrow B, Evers BM. Inflammation and the development of pancreatic cancer. Surg Oncol 2002;10:153–69.

[17] Mohseni Salehi Monfared SS, Vahidi H, Abdolghaffari AH, Nikfar S, Abdollahi M. Antioxidant therapy in the management of acute, chronic and post-ERCP pancreatitis: a systematic review. World J Gastroenterol 2009;15(36):4481–90.

[18] Cullen JJ, Mitros FA, Oberley LW. Expression of antioxidant enzymes in diseases of the human pancreas: another link between chronic pancreatitis and pancreatic cancer. Pancreas 2003;26(1):23–7.

[19] Komori S, Osada S, Yoshida K. Novel strategy with gemcitabine for advanced pancreatic. ISRN Oncol 2011:936893. http://dx.doi.org/10.5402/2011/93689.

[20] Bassoa D, Grecoa E, Fogara P, Puccib P, Flagiellob P, Baldoa G, et al.. Pancreatic cancer-associated diabetes mellitus: an open field for proteomic applications. Clin Chim Acta 2005;357:184–9.

[21] Furuta S, Jeng Y-M, Zhou L, Huang L, Kuhn I, Bissell MJ, et al.. IL-25 causes apoptosis of IL-25R – expressing breast

cancer cells without toxicity to nonmalignant cells. Sci Transl Med 2011;3:78ra31.
[22] Buning C, Genschel J, Weltrich R, Lochs H, Schmidt H. The interleukin-25 gene located in the inflammatory bowel disease (IBD) 4 region: no association with inflammatory bowel disease. Eur J Immunogenet 2003;30:329–33.
[23] Chang SH, Dong C. Signaling of interleukin-17 family cytokines in immunity and inflammation. Cell Signal 2011;23:1069–75.
[24] Swaidani S, Bulek K, Kang Z, Liu C, Lu Y, Yin W, et al.. The critical role of epithelial-derived Act1 in IL-17- and IL-25-mediated pulmonary inflammation. J Immunol 2009;182:1631–40.
[25] Saenz SA, Siracusa MC, Perrigoue JG, Spencer SP, Urban JF, Tocker JE, et al.. IL25 elicits a multipotent progenitor cell population that promotes T(H)2 cytokine responses. Nature 2010;464:362–1366.
[26] Fort MM, Cheung J, Yen D, Li J, Zurawski SM, Lo S, et al.. IL-25 induces IL-4, IL-5, and IL-13 and Th2-associated pathologies *in vivo*. Immunity 2001;15:985–95.
[27] Fallon PG, Ballantyne J, Mangan NE, Barlow JL, Dasvarma A, Hewett DR, et al.. Identification of an interleukin (IL)-25 - dependent cell population that provides IL-4, IL-5, and IL-13 at the onset of helminth expulsion. JEM 2006;203:1105–16.
[28] Zaph C, Du Y, Saenz SA, Nair MG, Perrigoue JG, Taylor BC, et al.. Commensal-dependent expression of IL-25 regulates the IL-23–IL-17 axis in the intestine. J Exp Med 2008;205:2191–8. http://dx.doi.org/10.1084/jem.2008072.
[29] Witowskia J, Ksiazeka K, Jörres A. Interleukin-17: a mediator of inflammatory responses. CMLS Cell Mol Life Sci 2004;61:567–79. http://dx.doi.org/10.1007/s00018-003-3228-z.
[30] Moseley TA, Haudenschild DR, Rose L, Reddi AH. Interleukin-17 family and IL-17 receptors. Cytokine Growth Factor Rev 2003;14:155–74.
[31] Gaffen SL. Structure and signalling in the IL-17 receptor family. Nat Rev Immunol 2009;9:556–67. http://dx.doi.org/10.1038/nri2586.
[32] Lee J, Ho WH, Maruoka M, Corpuz RT, Baldwin DT, Foster JS, et al.. IL-17E, a novel proinflammatory ligand for the IL-17 receptor homolog IL-17Rh1. J Biol Chem 2001; 276:1660–4.
[33] Kim MR, Manoukian R, Yeh R, Silbiger SM, Danilenko DM, Scully S, et al.. Transgenic overexpression of human IL-17E results in eosinophilia, B-lymphocyte hyperplasia, and altered antibody production. Blood 2002;100(7):2330–40.
[34] Lajoie-Kadoch S, Joubert P, Létuvé S, Halayko AJ, Martin JG, Soussi-Gounni A, et al.. TNF-a and IFN-g inversely modulate expression of the IL-17E receptor in airway smooth muscle cells. Am J Physiol Lung Cell Mol Physiol 2006;290:L1238–46. http://dx.doi.org/10.1152/ajplung.00301.2005.
[35] Maezawa Y, Nakajima H, Suzuki K, Tamachi T, Ikeda K, Inoue JI. Involvement of TNF receptor-associated factor 6 in IL-25 receptor signaling. J Immunol 2006;176:13–8.
[36] Morgan M, Thorburn J, Pandolfi PP, Thorburn A. Nuclear and cytoplasmic shuttling of TRADD induces apoptosis via different mechanisms. JCB 2002;157:975–84.
[37] Bryan NB, Dorfleutner A, Rojunasakul Y, Stehlik C. Activation of inflammasomes requires intracellular redistribution of the apoptotic speck-like protein containing a caspase recruitment domain. J Immunol 2009;18:3173–82.
[38] Dempsey PW, Doyle SE, He JQ, Cheng G. The signaling adaptors and pathways activated by TNF superfamily. Cytokine Growth Factor Rev 2003;14:193–209.
[39] Chen D, Zheng X, Kang D, Yan B, Xiaoyi Liu X, Gao Y, et al.. Apoptosis and expression of the Bcl-2 family of proteins and P53 in human pancreatic ductal adenocarcinoma. Med Princ Pract 2012;21:68–73. http://dx.doi.org/10.1159/000332423.
[40] Saleemy M, Kaury S, Kweony MH, Adhami VM, Afaq F, Mukhtar H. Lupeol a fruit and vegetable based triterpene, induces apoptotic death of human pancreatic adenocarcinoma cells via inhibition of Ras signaling pathway. Carcinogenesis 2005;26:1956–64. http://dx.doi.org/10.1093/carcin/bgi157.
[41] Kolls JK, Lindén A. Interleukin-17 family members and inflammation. Immunity 2004;21:467–76.
[42] Schneider C, Schmidt T, Ziske C, Tiemann K, Lee KM, Uhlinsky V, et al.. Tumour suppression induced by the macrophage activating lipopeptide MALP-2 in an ultrasound guided pancreatic carcinoma mouse model. Gut 2004;53:355–61. http://dx.doi.org/10.1136/gut.2003.02600.
[43] Kottke T, Pulido J, Thompson J, Sanchez-Perez L, Chong H, Calderwood S, et al.. Anti tumor immunity can be uncoupled from autoimmunity following Hsp70-mediated inflammatory killing of normal pancreas. Cancer Res 2009;69(19):7767–74. http://dx.doi.org/10.1158/0008-5472.CAN-09-1597.
[44] Mayorek N, Naftali-Shani N, Grunewald M. Diclofenac inhibits tumor growth in a murine model of pancreatic cancer by modulation of VEGF levels and arginase activity. PLoS One 2010;5:e12715.
[45] Fischer AH, Jacobson KA, Rose J, Zeller R. Hematoxylin and eosin staining of tissue and cell sections. Cold Spring Harbor Protoc 2008. http://dx.doi.org/10.1101/pdb.prot4986.
[46] Soleimani M, Nadri S. A protocol for isolation and culture of mesenchymal stem cells from mouse bone marrow. Nat Protoc 2009;4:102–6.
[47] Nadri S, Soleimani M. Isolation of CD34+ mesenchymal stem cells from mouse bone marrow. SJIBTO 2007;4:143–51.
[48] Mazaheri T, Esmaeilzadeh A, H.KH. Mirzaei M. Introducing the immunomodulatory effects of mesenchymal stem cells in an experimental model of Behcet's disease. J Med Hypotheses Ideas 2012;6:23–7.
[49] Wei WT, Chen H, Wang ZH, Ni ZL, Liu HB, Tong HF, et al.. Enhanced antitumor efficacy of gemcitabine by evodiamine on pancreatic cancer via regulating PI3K/Akt pathway. Int J Biol Sci 2012;8:1–14.
[50] Fulda S. Targeting apoptosis signaling in pancreatic cancer. Cancer 2011;3:241–51, http://dx.doi.org/10.339/cancers301024.
[51] Loebinger MR, Sage EK, Janes SM. Mesenchymal stem cells as vectors for lung disease. Proc Am Thorac Soc 2008;5:711–6. http://dx.doi.org/10.1513/pats.200801-009AW.